ERG REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Head and neck cancer (squamous cell carcinoma) – cetuximab (review of TA 172) [ID1016]

CDF rapid reconsideration

Confidential until published

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1 INTRODUCTION

The National Institute for Health and Care Excellence (NICE) is in the process of assuming responsibility for the Cancer Drugs Fund (CDF). The CDF provided a mechanism for some cancer treatments which failed to receive a positive recommendation when originally appraised for clinical and cost effectiveness for general use in the NHS, to be provided, on a case-by-case basis to selected patients referred to the CDF by their clinician. As part of the transition, a number of historic technology appraisal decisions are being rapidly reconsidered to determine the future status of treatments currently provided only through the CDF, i.e. whether they may now be recommended for general use, continue within the scope of the revised CDF scheme, or not be provided at all through the NHS. The Liverpool Reviews and Implementation Group (LR*i*G) at the University of Liverpool has been commissioned to review the company submission (CS) to assist a NICE Appraisal Committee (AC) in reconsideration of the use of cetuximab (Erbitux®) for the treatment of recurrent/metastatic head and neck cancer. The original Single Technology Appraisal (STA) was conducted in 2008. The final NICE guidance was issued in April 2009 and did not recommend the use of cetuximab in this patient population.

1.1 Context and approach to rapid reconsideration

To allow these rapid reconsideration exercises to proceed with the minimum risk of delay, the expected procedures have been restricted in scope for the company making a resubmission and for the Evidence Review Group (ERG) who is tasked with providing an independent assessment of the Company Submission (CS). It is assumed that the primary clinical effectiveness data will remain essentially unchanged from the original appraisal and therefore no additional clinical evidence will be accepted by NICE. The cost effectiveness analyses included in the CS needs to reflect the assumptions that determined the most plausible incremental cost-effectiveness ratio(s) (ICERs) as identified in the published guidance. It is anticipated that the main areas to be considered by the AC will relate to changes in the costs associated with treatment including any special NHS pricing agreements that have been agreed since the original STA was carried out.

2 SPECIFIC DETAILS OF THIS RAPID RECONSIDERATION

2.1 Considerations from existing guidance and new CS

As with the original submission the primary data considered in the CS comes from the EXTREME trial.[1] Details of the trial characteristics are presented in Table 1

Table 1 EXTREME trial characteristics

Design	Intervention	Inclusion criteria (main)	Exclusion criteria (main)	Outcomes
Multicentre, European phase III open label Patients (n=442) Randomisation 1:1 ratio Stratification according to receipt or non-receipt of previous CTX and KPS score	Cetuximab plus CTX (cisplatin plus 5-FU or carboplatin plus 5-FU) n=222 CTX n=220 Oral cavity patients Cetuximab plus CTX 46/222 (21%) CTX 42/220 (19%)	18 years +; Histologically or cytologically confirmed recurrent and/or metastatic SCCHN; ineligibility for local therapy; At least one lesion bio-dimensionally measurable; KPS ≥70; Adequate hematologic, renal, hepatic function; Tumour tissue available for evaluation of EGFR expression	Surgery or irradiation within the previous 4 weeks; Previous systemic CTX unless part of multimodal treatment for locally advanced disease completed > 6 months before study entry; Nasopharyngeal carcinoma; Concomitant anticancer therapies	Primary: OS (time from randomisation to death) Secondary : PFS (time from randomisation to radiologic confirmation of disease progression, or death from any cause within 60 days after the last assessment or randomisation, whichever came first); A variety of response rates; Quality of life

CTX=chemotherapy treatment; OS= overall survival; PFS = progression free survival; TTF = time to treatment failure; SCCHN=squamous cell carcinoma of the head and neck; KPS=Karnofsky performance status; EGFR=epidermal growth factor receptor

It is worth noting the clinical issues addressed as part of the Appraisal Committee (AC) discussion and included in the existing guidance[2] that are addressed as part of the CS that has been received. These include limiting consideration to the subgroup of patients with oral cavity carcinoma and a case for end of life criteria and are outlined in Table 1

The CS makes reference to more up-to-date five year survival data available from the EXTREME trial and presented as an abstract in 2014.[3] This data is for the whole population of the EXTREME trial and does not provide any data related to the specific sub group of patients with oral cavity carcinoma.

Table 2 Considerations in existing guidance and CS

NICE guidance[2]	Company position[4]	Evidence in CS for this position
Subgroup – oral cavity Clinical specialists informed the AC; 'that patients with tumours in the oral cavity have a relatively favourable prognosis compared with the average prognosis for recurrent and/or metastatic SCCHN. (page 13) 'The Committee accepted that the trial demonstrated the efficacy of cetuximab plus platinum-based chemotherapy in patients with recurrent and/or metastatic SCCHN, but it was not persuaded that the evidence supported using the subgroup estimate for clinical effectiveness in the economic model.' (page 14)	The CS also makes a case for the poor prognosis for this patient population. CS states that they focused on the oral cavity subgroup because 'there is little chance of becoming cost effective in the overall population' page 12	Combined data from two RCTS of patients (n-399) with recurrent head and neck cancer treated with cisplatin-based combination chemotherapy[5] 'median survival in patients with oral cavity or hypopharyngeal cancers was 0.52 years compared to 0.70 years in patients with other head and neck cancers (p=0.04)' page 9 of CS Reference to clinical expert testimony – data held by the company and not available to the ERG
End of life consideration 'The Committee considered the criteria only in relation to the estimate of overall survival for the cohort population because it did not consider the subgroup data to be robust' (page 16) The committee considered that the life expectancy for these patients was likely less than 24 months. However, 'it was also aware that the predicted life years gained from the economic modelling for this group was 0.187, reflecting a gain in overall survival of approximately 2.2 months. The Committee therefore did not consider that this estimate of gain in overall survival was in keeping with the criteria relating to extension of life' (pages 16-17)	Outcomes demonstrate end of life benefit shown in EXTREME trial data	Data from EXTREME[1] 'In the context of end of life treatment, the EXTREME trial shows that patients with an oral cavity tumour show both a significant incremental delay in progression (median PFS of 3.3 months) and incremental improvement in overall survival (median OS of 6.6 months) beyond the 3 months required to meet the criteria.' (page 59) Life years gained for oral cavity patients (Table10 – page 47) 1.13 years for Cetuximab plus CTX versus 0.58 years for CTX patients Additional data from a single arm trial of patients (n=54) that received combination treatment and reported median OS of 14 months.[6]

2.2 Cetuximab drug costs

The company proposes a new cetuximab price of [redacted], which incorporates a revised patient access scheme (PAS). The company states that this new price represents a [redacted] from cetuximab's list price (£178.10/20ml [100mg vial] and £795.10/100ml [500mg vial]). However, the previous acquisition cost to the NHS was £136.50/20ml and £682.50/100ml vial by means of a procurement discount.

It is worth noting that '[redacted]'(page 21)

3 MODEL ALTERATIONS

The CS is based on a modified version of the decision model used in the original technology appraisal (TA172), with amendments to address some of the issues highlighted by the ERG in their 2008 report and specifically mentioned by the Appraisal Committee in Section 3.15 of the ACD.[7]

- the absence of a mid-cycle correction
- restricting analysis to the 24 months period of available follow-up data
- combining mean utility estimates across treatment arms
- using UK audit data for mean body-surface area (BSA) for calculating drug costs
- using a recent common price base for all hospital and care costs

3.1 Implementing ERG recommended amendments

3.1.1 Continuity correction

Ideally a decision model should be able to accommodate accurately events occurring at any time following randomization. However, in practise this leads to very large and unwieldy models depending on the degree of precision required (daily/hourly/other). The compromise generally used involves dividing time into discrete segments and then updating all variables and results at each discrete time point. Inevitably this provides only an approximation to the true costs and outcomes of any treatment as important changes can take place at any time between the chosen model discrete times. To compensate for this imprecision it is common practice to introduce a 'continuity correction' to smooth the effects of changes occurring between modelled time points.

The original version of the company model did not include any such continuity corrections. The ERG recommended in 2008 the use of 'mid-cycle' corrections which involve estimating both costs and outcomes across each time period in the model by averaging the determining variable (e.g. patients alive, patients on treatment, etc.) across the start and end points of each period. In their revised model the company have chosen not to use such a mid-cycle correction, but have instead applied a simpler 'half-cycle correction' which applies a single alteration to each estimated model output based on only the first and last time point covered by the model. The 'half-cycle correction' is necessarily less accurate than the 'mid-cycle' correction method since it does not follow the time-varying pattern of each model variable across many years, and therefore fails to reflect accurately the effect of discounting both cost and outcome results over the duration of the assessment.

The ERG has investigated the differential effects of these two methods on some of the variables in the current version of the company model, and concluded that although there is evidence of differences, these are relatively minor compared with other issues identified below, and therefore do not warrant further attention.

3.1.2 Limited model duration

The original company model projected the then available clinical evidence (a maximum of 24 months follow-up) for a lifetime in accordance with the NICE scope. However, the AC were concerned that extrapolation of limited short-term follow-up trends over extended periods may lead to unreliable cost-effectiveness estimates.

The current company model is calibrated using extended 5-year follow-up data, so that in part uncertainties evident to the AC previously in this regard no longer apply.

3.1.3 Pre-progression utility estimates

The utility value applied to time spent with stable disease or with response to treatment prior to disease progression is a critical model variable, as the majority of patient survival benefit seen in the EXTREME trial occurred prior to disease progression.

No utility data were collected in the EXTREME trial. The EORTC quality of life survey was used in the trial but response rates were generally poor. A published algorithm was used to estimate UK-equivalent EQ-5D utility estimates from the available EORTC survey data. The uncertainty (confidence interval) for these estimates is very wide, so that the observed differences in mean utility estimates for patients either before or after disease progression are not statistically significant. Both the company and the ERG agreed that a single overall utility estimate is appropriate for the post-progression health state. However, the company

argue that separate treatment-specific utility estimates should be used pre-progression on two grounds:

- that there are better response rates for cetuximab than for the comparator
- that cetuximab has a better adverse event profile

The ERG presented evidence to suggest that any utility differences attributable to adverse events would be very small, and inconsequential compared to the difference claimed for cetuximab.

It is also worth pointing out that the difference in pre-progression utility estimates is reduced but not eliminated in the corresponding post-progression utility estimates where differences in pre-progression response rates and adverse events largely lose relevance. This suggests that the treatment-specific non-significant utility differences in the trial data are simply explained as random effects of case-mix variation.

3.1.4 Estimating drug costs

The company has not altered its method of estimating the acquisition cost of drugs (including cetuximab), relying on the mean BSA value recorded in the EXTREME trial and making no adjustment for the gender differences in BSA and other body metrics observed in general population surveys, and in the published UK audit study cited by the ERG (Sacco, et al[8]). The company method of costing does not take any account of the variation in BSA within the treated population. The company suggests that the BSA seen in the specific trial population will not correspond to the BSA distribution in the wider head & neck cancer UK population.

3.1.5 Price base for hospital and care costs

The company has updated all relevant costs and prices to a common 2014/15 price base.

3.2 ERG analysis and amendments

The ERG submitted a set of clarification requests to NICE for the company to provide important information specific to the Oral Cavity subgroup of the EXTREME clinical trial. In particular, these included full Kaplan-Meier (K-M) analysis results showing K-M survival estimates at each event time, for both treatment arms in the EXTREME trial for overall survival, and progression-free survival using the most recent data cut and based on the investigator assessment of disease progression. These requests were aimed at validating the company approach to modelling survival outcomes, and if necessary allowing alternative interpretations of the trial evidence to be assessed.

3.2.1 Progression-free survival

Analysis by the ERG of the latest EXTREME trial PFS K-M data suggested that the simplest and most accurate representation of the data in both trial arms is to assume a constant progression hazard over time (i.e. a straight-line trend for the cumulative hazard plot in Figure 1. This is in contrast to the company's use of Weibull functions for both trial arms which show a consistent bias towards over-estimating PFS for both treatment arms (Figure 2).

In order to recognise the primacy of original trial data over any modelled projection, the ERG has chosen to use the EXTREME trial K-M data directly in the model, and only apply the modelling projection at the end of the available trial data (after 13 months for the Cetuximab + CTX arm, and after 6 months for the CTX only arm.

The ERG method of modelling lifetime PFS results in a slightly increased mean estimated PFS net gain in mean PFS of 4.09 months (Table 3), and a reduction of £1,067 per QALY gained from the base case estimated deterministic ICER.

Table 3 Comparison of PFS estimates using company and ERG methods

Estimation method	Cetuximab+CTX (months)	CTX only (months)	PFS gain (months)
Company base case	7.52	3.49	+ 4.03
ERG PFS analysis	7.31	3.22	+ 4.09

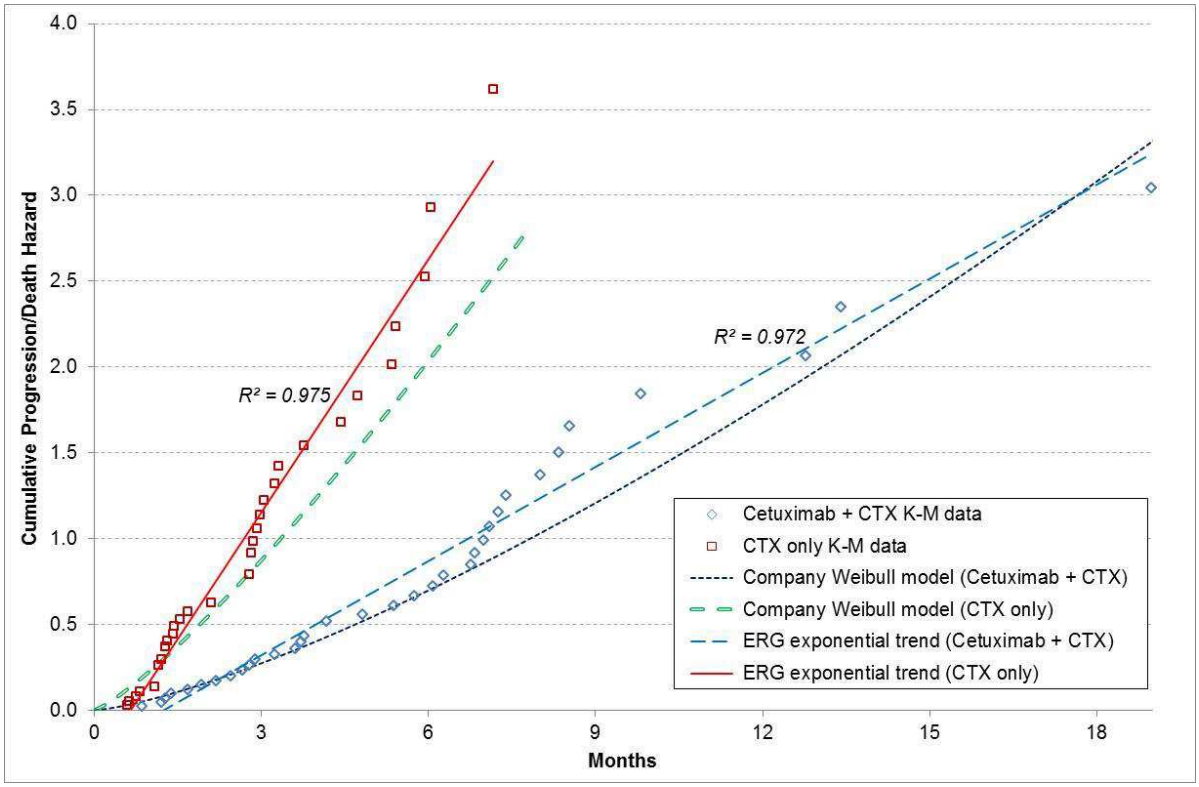

Figure 1 Comparison of Company and ERG modelling of PFS cumulative hazard

CTX = chemotherapy; K-M = Kaplan-Meier analysis

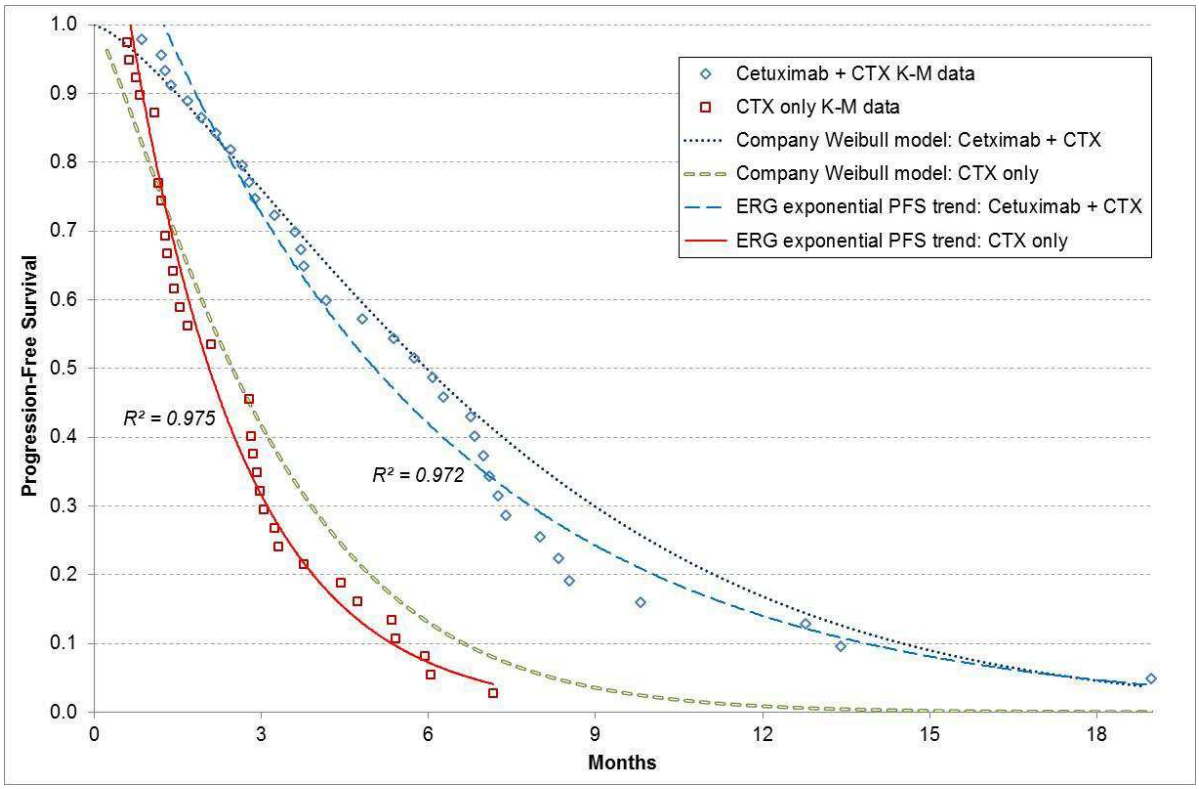

Figure 2 Comparison of Company and ERG modelling of PFS

CTX = chemotherapy; K-M = Kaplan-Meier analysis

3.2.2 Overall survival

Analysis by the ERG of the latest EXTREME trial OS K-M data suggested a different pattern of temporal trends for OS. At 7-8 months there is evidence of the establishment of similar constant progression hazard trends over time (i.e. straight-line long-term trends in the cumulative hazard plot in Figure 3). This is in contrast to the company's use of Weibull functions for both trial arms; in particular, there is a substantial deviation from trial data in the comparator arm after about 5 months.

Figure 4 and Table 4 show that the ERG alternative approach to reflecting the long term survival of patients in the oral cavity subgroup, results in slightly reduced survival in the Cetuximab+CTX arm and a small improvement in OS for the CTX arm, so that the OS gain attributable to cetuximab is reduced from 6.72 months to 6.40 months. This has the effect of increasing the estimated deterministic ICER by £1,492 per QALY gained

Table 4 Comparison of OS estimates using company and ERG methods

Estimation method	Cetuximab+CTX (months)	CTX only (months)	OS gain (months)
Company base case	13.68	6.95	+ 6.72
ERG OS analysis	13.51	7.12	+ 6.40

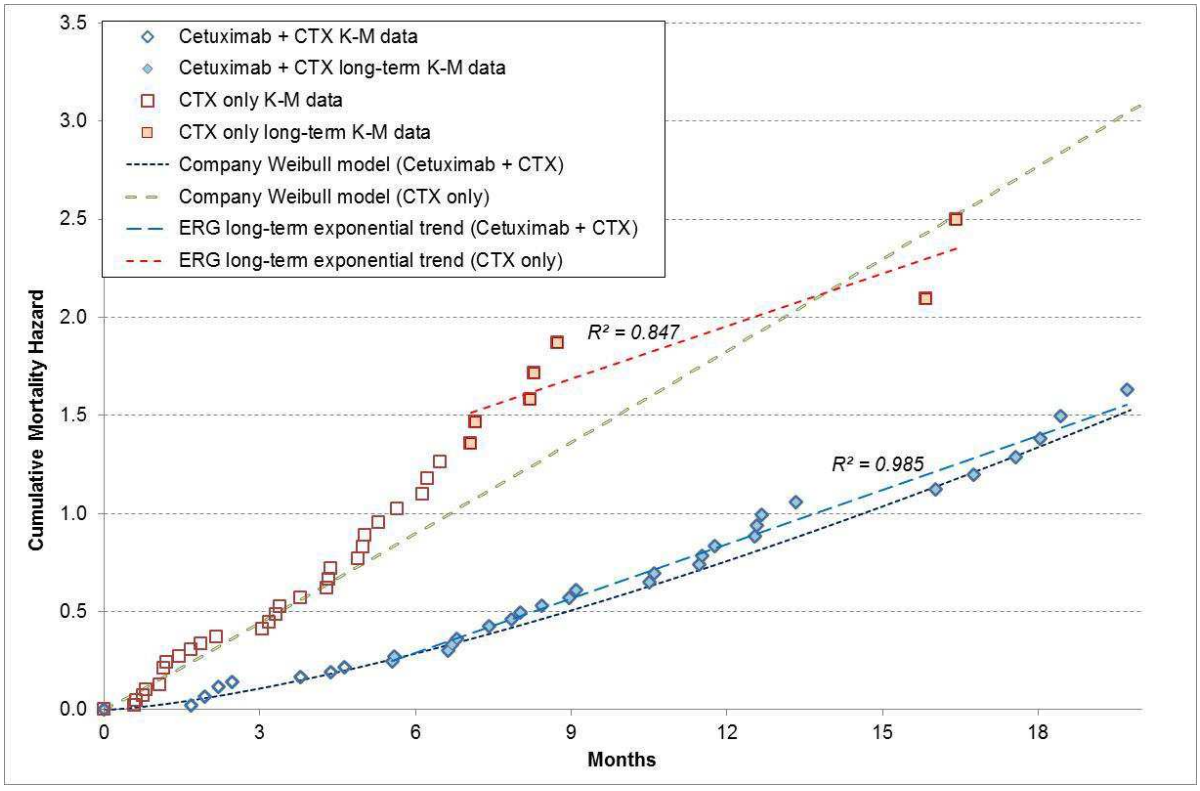

Figure 3 Comparison of Company and ERG modelling of OS cumulative hazard

CTX = chemotherapy; K-M = Kaplan-Meier analysis

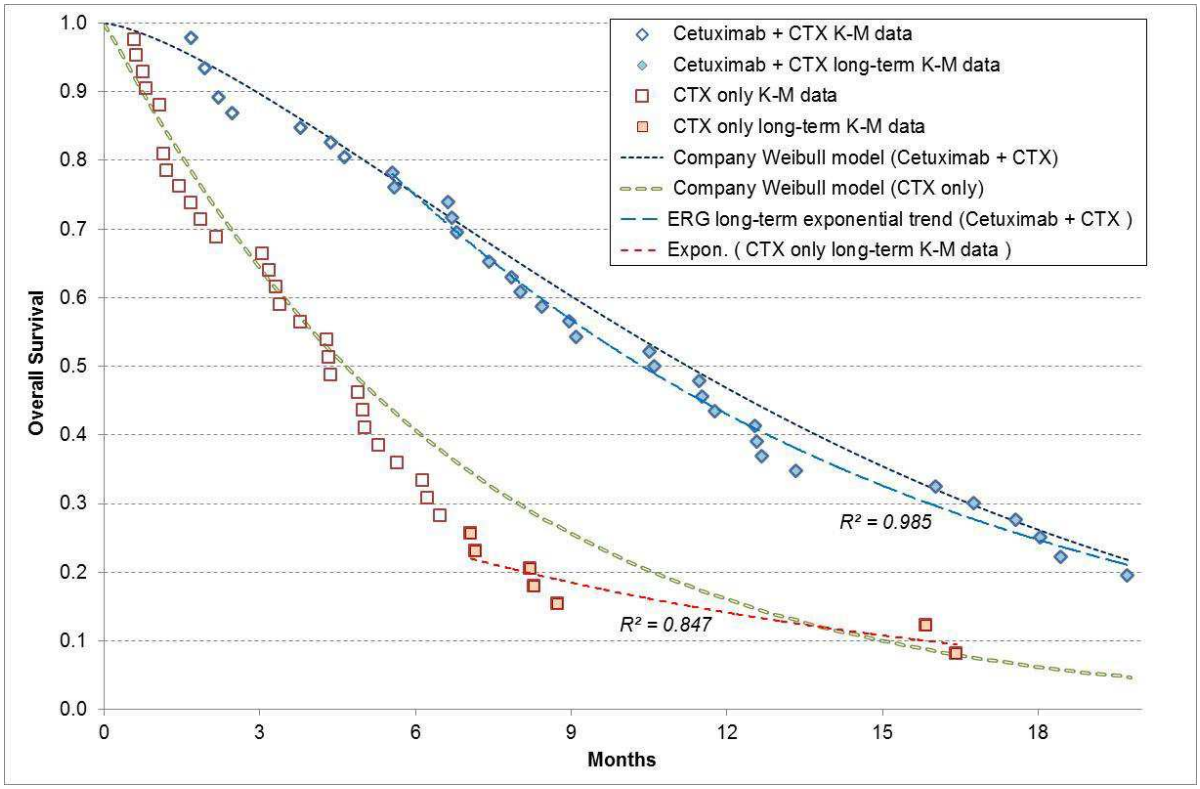

Figure 4 Comparison of Company and ERG modelling of OS

CTX = chemotherapy; K-M = Kaplan-Meier analysis

3.2.3 Post-progression survival

The ERG has not been able to estimate post-progression survival directly from trial data. However, the difference between OS and PFS estimates implies that between 40% (company model) and 36% (ERG estimate) of the OS estimate gain from treatment with cetuximab occurs after confirmed disease progression. This extent of survival gain taking place after patients' condition has deteriorated and the allocated active treatment has been terminated is unusual, and implies that some additional survival benefit can accrue in this patient group.

3.2.4 Drug acquisition costs

The ERG has re-estimated the acquisition cost to the NHS of the various products licensed for use in treating patients with head and neck carcinoma. Treatments prescribed according to a patient's BSA have been estimated for a typical UK population using the mean and standard deviation BSA for selected patients with head and neck cancer undergoing chemotherapy at three UK cancer cancers (Sacco et al.[8]). These values have been re-estimated to exclude all patients for whom the treatment intention was recorded as adjuvant, neo-adjuvant or palliative.

In addition it is necessary to apply a gender ratio when calculating a weighted average cost per cycle. The ERG has estimated costs based on three sources:

- the EXTREME clinical trial (90.3% males: 9.7% females)
- the UK audit study (73.3% males: 26.7% females)
- National Cancer Intelligence Network[9] estimate (60% males: 40% females)

Table 5 summarises the four options available to explore the sensitivity of cost-effectiveness to different assumptions. All ERG estimates of the cost of cetuximab exceed those of the company, whereas almost all other costs are lower when the ERG method is employed.

Applying the ERG estimated drug costs results in the deterministic ICER estimate increasing by £1,923 per QALY gained (trial gender balance), £1,523 (UK audit study gender balance) and £1,211 per QALY gained (NCIN[9] population estimated gender balance). The first would be preferred to ensure consistency with other trial data, and the second to match a relevant UK patient population.

Table 5 Estimated acquisition cost of 21 day cycle of treatment

Treatment	Company base case	ERG estimate using trial gender balance	ERG estimate using UK audit gender balance	ERG estimate using NCIN gender balance
Cetuximab (cycle 1)	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab (cycles 2+)	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	£25.06	£21.35	£21.15	£21.00
5-FU	£29.49	£10.50	£10.40	£10.31
Bleomycin	£93.36	£91.11	£91.11	£91.11
Docetaxel	£24.78	£24.20	£24.20	£24.20
Methotrexate	£9.72	£6.30	£6.30	£6.30
Paclitaxel	£25.48	£21.65	£21.65	£21.65
Vinorelbine	£89.32	£95.68	£95.68	£95.68

3.2.5 Pre-progression utility values

As described above (Section 3.1.3) the ERG remains of the view that there is no strong evidence to support use of treatment-specific utility values to be used in the decision model. It is most likely that the difference in estimated values based on limited transformed trial quality of life data is largely an artefact of random variation. It is noteworthy that the calculations used to derive these estimated values are based on available data from the

whole trial population. If only EORTC survey responders from the 20% of the whole trial population with oral cavity carcinoma had been used instead, the balance of estimated pre-progression utility estimates may have been very different in either direction.

When a single common utility value is used, the estimated deterministic ICER increases by £2,883 per QALY gained.

3.2.6 Adjustment to match model predicted and trial use of cetuximab

An unusual feature of the company model is a logic 'switch' which applies a poorly explained alteration to the cost of cetuximab treatment based on a failure to reconcile the number of vials of cetuximab predicted by the company model with the number expected on the basis of recorded use during the trial. The details of the development of this feature are obscure, and it is not possible to assess whether this has been correctly estimated or not. Of particular concern is that the use of this adjustment presumes that there is a serious flaw in the company model which cannot be traced or corrected. There is no mention of the alternative possibility that accounting for trial medication issued and used may have been the source of the discrepancy. Either way, there must be serious concern that either the model or some aspects of trial data collection are unreliable.

Without any additional explanation or supporting trial evidence, it seems reasonable to assume that the attempt to reconcile vial numbers is misdirected, and that modelled cost estimates based on more traditional methods of estimating patient numbers on treatment should be relied upon. In other words the ERG considers that the 'adjustment' feature of the model should be disabled when estimating cost-effectiveness of cetuximab. This has the effect of increasing the estimated deterministic ICER by £12,002 per QALY gained.

3.2.7 Cisplatin vs carboplatin

In the original ERG report for TA172,[10] it was observed that"

> "The EXTREME trial allowed clinicians a choice between cisplatin and carboplatin for platinum-based CTX, and the base case model analysis uses the observed trial proportions (31.7% carboplatin in the intervention arm and 37.2% in the control arm). Clinical advice indicates that cisplatin is used in almost all cases in the UK."

On this basis the ERG consider it appropriate to assume that 100% patients receiving platinum therapy with receive cisplatin. This has only a minor effect by reducing the estimated deterministic ICER by £25 per QALY gained.

Details of all model amendments are provided in the Appendix.

4 RESULTS

Table 6 summarises the cost effectiveness results obtained using the revised decision model submitted by the company, together with results using the various ERG corrections and revisions described above. The ERG's preferred options result in an estimated ICER of [redacted] per QALY gained for cetuximab in combination with chemotherapy compared with standard chemotherapy for patients with recurrent or metastatic oral cavity carcinoma, an increase of more than [redacted] per QALY gain relative to the base case ICER in the company submission.

Table 6 Deterministic cost effectiveness (Cetuximab + CTX versus CTX): ERG revisions to company base case

Model scenario ERG revision	Cetuximab+CTX			CTX			Incremental			ICER	ICER
	Cost	QALYs	Life years	Cost	QALYs	Life years	Cost	QALYs	Life years	Per QALY gained	Change
A. Company base case	[redacted]	***0.673***	***1.139***	***£10,299***	***0.319***	***0.579***	[redacted]	***0.353***	***0.560***	[redacted]	-
R1) ERG revised drug costs: a)trial gender mix b)UK audit gender mix c)NCIN gender mix	[redacted]	0.673	1.139	£10,219 £10,218 £10,217	0.319	0.579	[redacted]	0.353	0.560	[redacted]	[redacted]
R2) ERG revised PFS estimates	[redacted]	0.670	1.139	£10,478	0.317	0.579	[redacted]	0.353	0.560	[redacted]	[redacted]
R3) ERG revised OS estimates	[redacted]	0.664	1.126	£10,409	0.325	0.593	[redacted]	0.339	0.533	[redacted]	[redacted]
R4) Apply 100% cisplatin use	[redacted]	0.673	1.139	£10,244	0.319	0.579	[redacted]	0.353	0.560	[redacted]	[redacted]
R5) Common pre-progression utility value	[redacted]	0.661	1.139	£10,299	0.325	0.579	[redacted]	0.336	0.560	[redacted]	[redacted]
R6) Disable cetuximab reconciliation adjustment	[redacted]	0.673	1.139	£10,299	0.319	0.579	[redacted]	0.353	0.560	[redacted]	[redacted]
B. ERG revised base case A+R1a/b/c, R2 – R6	[redacted]	***0.650***	***1.126***	***£10,449 £10,447 £10,446***	***0.327***	***0.593***	[redacted]	***0.323***	***0.533***	[redacted]	[redacted]

5 REFERENCES

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APPENDIX: ERG AMENDMENTS MADE TO COMPANY MODEL

Most revisions are activated by a logic switch with 0 = unchanged, 1-3 = apply ERG specified modification.

Logic switches are indicated by range variables created in the 'Results' worksheet Mod_*n* where n = 1 – 4.

Summary results as used to transfer to the ERG report are shown in range 'Results'!C141:L141.

ERG Revision	Associated detail	Implementation details
R1. ERG revised drug acquisition costs with gender mix (Multi-value switch Mod_1)	Recalculation workbook "Dosing calculations final"xlsx	In Sheet 'Unit costs' A table of ERG estimated costs per cycle for each of three sources of evidence for patient gender mix has been created in the range M9:O28 Detailed derivation of each estimate is shown in workbook XXXX. **Replace** formula in cell G11 by =CHOOSE(Mod_1+1,F11*C11,M11,N11,O11) **Copy** formula in cell G11 and paste into range G12:G16 **Copy** formula in cell G11 and paste into range G23:G24 **Copy** formula in cell G11 and paste into range G26:G28
R2. ERG PFS estimates (Binary switch Mod_2)	ERG survival estimates for both PFS and OS are included as a new worksheet 'ERG_survival'	In Sheet 'Markov-Txarm1', **Replace** formula in cell L7 by =IF(Mod_2=1,ERGsurvival!C5,EXP(-B18 *E7^B17)) **Copy** formula in cell L7 and paste to range L8:L207 In Sheet 'Markov-Txarm2', **Replace** formula in cell L7 by =IF(Mod_2=1,ERGsurvival!E5,EXP(-B18 *E7^B17)) **Copy** formula in cell L7 and paste to range L8:L207
R3. ERG OFS estimates (Binary switch Mod_3)	ERG survival estimates for both PFS and OS are included as a new worksheet 'ERG_survival'	In Sheet 'Markov-Txarm1', **Replace** formula in cell K7 by =IF(Mod_3=1,ERGsurvival!D5,EXP(-B12 *E7^B11)) **Copy** formula in cell K7 and paste to range K8:K207 In Sheet 'Markov-Txarm2', **Replace** formula in cell K7 by =IF(Mod_3=1, ERGsurvival!F5, EXP(-B12 *E7^B11)) **Copy** formula in cell K7 and paste to range K8:K207
R4. Set platinum therapy to 100% cisplatin (Binary switch Mod_4)	None	In Sheet 'Resource use and Cost', **Replace** formula in cell C12 by =IF(Mod_4=1,0,69/(149+69)) **Replace** formula in cell C13 by =IF(Mod_4=1,1,149/(149+69)) **Replace** formula in cell I15 by =IF(Mod_4=1,0,80/(80+135)) **Replace** formula in cell I16 by =IF(Mod_4=1,1,135/(135+80))
R5. Pre-progression utility set to common value in both arms	None	Manually set 'Utilities!C18' drop-down menu to "Overall"
R6. Disable cetuximab usage adjustment	None	Manually set 'Resource use and cost'!C27 drop-down menu to "No"